EXHIBIT 3

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Aspirin Compared with Acetaminophen in the Treatment of Fever and Other Symptoms of Upper Respiratory Tract Infection in Adults: A Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel-Group, Single-Dose, 6-Hour Dose-Ranging Study

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ABSTRACT

Background: Aspirin (acetylsalicylic acid) and acetaminophen (paracetamol) are frequently used to treat fever and other symptoms of upper respiratory tract infection (URTI). Both are available over the counter for use at the standard recommended doses of 500 and 1000 mg per single use.

Objective: This study investigated the efficacy, safety profiles, and tolerability of aspirin 500 and 1000 mg and acetaminophen 500 and 1000 mg compared with placebo in adult patients with acute febrile URTI of suspected viral origin.

Methods: This was a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group trial conducted in Ukraine and Russia. Patients with URTI and acute fever of ≥38.5°C received a single dose of aspirin 500 or 1000 mg, acetaminophen 500 or 1000 mg, or matching placebo. Oral body temperature was measured in the clinic at specified time points up to 6 hours after dosing. The intensity of other symptoms of URTI was rated by patients at baseline and at 2, 4, and 6 hours after dosing (scale from 0 = none to 10 = severe). The primary efficacy measure was the AUC for the change in orally measured body temperature from the time of treatment (baseline) to 4 hours after dosing. Secondary outcome measures included the change in body temperature from baseline to specified time points between 0.5 and 6 hours after dosing, the difference between baseline and the lowest measured body temperature, the time to the lowest measured body temperature, and the intensity of other symptoms of URTI (ie, headache, sinus sensitivity to percussion, sore throat, achiness, and feverish discomfort). Tolerability was monitored by recording of adverse events.

Results: Three hundred ninety-two patients were enrolled (78 in both aspirin groups, 79 in both acetaminophen groups, 78 in the placebo group). Demographic and baseline characteristics were comparable in the 5 groups; 51% of patients were male, with a mean age of 37.4 years and a mean body weight of 74.3 kg. The AUC values for the change in body temperature 0 to 4 hours after dosing were 3.18 (95% CI, 2.78–3.57) for aspirin 500 mg, 4.26 (95% CI, 3.84–4.68) for aspirin 1000 mg, 3.13 (95% CI, 2.77–3.49) for acetaminophen 500 mg, 4.11 (95% CI, 3.73–4.49) for acetaminophen 1000 mg, and 0.76 (95% CI, 0.38–1.13) for placebo. In terms of the primary efficacy variable, all active treatments were significantly superior to placebo ($P < 0.001$, 1-sided t test), with no significant differences between them. Reductions in body temperature were significantly greater with the 1000-mg doses of both active treatments compared with the 500-mg doses ($P < 0.001$, 1-sided t test). The mean maximum temperature reductions were 1.32°C, 1.25°C, 1.67°C, 1.71°C, and 0.63°C in the respective treatment groups. Significant reductions were seen in the

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mean intensity of headache, achiness, and feverish discomfort with all active treatments at most time points ($P < 0.001$), but not in sinus sensitivity to percussion or sore throat. All treatments were equally well tolerated, and no clinically significant adverse events occurred.

Conclusions: In this single-dose study, aspirin 500 and 1000 mg and acetaminophen 500 and 1000 mg were more effective against fever and other symptoms of URTI than placebo. Both active treatments showed dose-related efficacy, and there was no significant difference between equal doses of the 2 agents. Safety profiles and tolerability were also comparable between treatments. (*Clin Ther.* 2005;27:993–1003) Copyright © 2005 Excerpta Medica, Inc.

Key words: aspirin, acetylsalicylic acid, acetaminophen, paracetamol, fever, headache, upper respiratory tract infection.

INTRODUCTION

Fever associated with upper respiratory tract infection (URTI) of suspected viral origin and influenzalike symptoms (eg, headache, frontal and maxillary sinus sensitivity to percussion, sore throat, achiness, and feverish discomfort) are prevalent during the common cold season. Elevated body temperature is a prominent sign of infection. Although fever is sometimes as high as 41°C, it more commonly ranges between 38°C and 40°C. It typically lasts for 3 days, but its duration may range from 1 to 5 days. Cough and malaise may persist for 1 to 2 weeks.[1] Maintaining normal daily activity by reducing fever and influenzalike symptoms is important to patients, and they may use over-the-counter (OTC) antipyretics for this purpose. Aspirin (acetylsalicylic acid) and acetaminophen (paracetamol) are among the most commonly used drugs in these circumstances.[2] Whereas both agents have analgesic activity, only aspirin has additional anti-inflammatory properties.[2] Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits cyclooxygenase and prostaglandin biosynthesis and consequently reduces pain, inflammation, and fever.[3–7] A central and peripheral mechanism of action has been proposed for acetaminophen.[2,8,9] For fever and pain, 500 and 1000 mg are commonly used single doses of both agents, corresponding to 1 or 2 tablets. When these drugs are purchased OTC, 1000 mg is the maximum recommended single dose.

Despite frequent use of these agents in the treatment of fever, a search of MEDLINE from 1990 through 2004 using the terms *aspirin, acetaminophen, paracetamol, fever,* and *upper respiratory tract infection* located only a small number of recent randomized, controlled clinical trials on the antipyretic efficacy of these drugs in adult patients. Although no current head-to-head comparisons of aspirin and acetaminophen are available, health care professionals and patients often believe that acetaminophen is more effective for fever and has fewer adverse effects than aspirin, and that aspirin is more effective in relieving pain.

This placebo-controlled, dose-ranging study was conducted to compare the efficacy and tolerability of single 500- and 1000-mg doses of aspirin and acetaminophen in the relief of fever and other symptoms of URTI.

PATIENTS AND METHODS

Inclusion and Exclusion Criteria

Men and women between the ages of 18 and 65 years with an acute, uncomplicated, febrile URTI of suspected viral origin were eligible for inclusion. The URTI had to have been present for no more than 5 days, orally measured body temperature (at the clinic) had to be between 38.5° and 40°C, and other symptoms of URTI (ie, myalgia/achiness, headache, frontal and maxillary sinus sensitivity to percussion, sore throat, feverish discomfort, sneezing, rhinorrhea, nasal congestion, cough, chills, sweating, and fatigue) had to be present.

Patients with physical findings consistent with a diagnosis of pneumonia, otitis media, bacterial sinusitis, or any other bacterial infection of the respiratory tract requiring antibiotics or other therapeutic intervention by a physician; those who were receiving current antibiotic treatment or who had received antibiotic agents during the previous week; those with a history of asthma or hypersensitivity to acetylsalicylic acid, salicylates, or other NSAIDs or acetaminophen; and those with peptic ulceration or gastric bleeding, hemorrhagic diathesis, hepatic and/or renal dysfunction, Gilbert's disease, or Quincke's edema were excluded. Any other acute or chronic disease that in the opinion of the investigator, could interfere with the patient's health and well-being during the conduct of the study or with evaluation of the data, as well as any condition that might interfere with the gastrointestinal

absorption of the study medication, was also considered an exclusion. Pregnant or lactating women, individuals with known drug dependency or alcohol abuse, and patients who had participated in another clinical study within the previous 4 weeks were not recruited.

The following concomitant medications were not allowed: short-acting antipyretic drugs, including acetaminophen, aspirin, and ibuprofen, within 24 hours before intake of study medication; long-acting antipyretic drugs (including naproxen and other NSAIDs), cold medications containing antipyretic drugs, and glucocorticoids or corticosteroids within 48 hours before intake of study medication; anticoagulant drugs, heparin, tranquilizers, sedatives, and psychotropic drugs within 72 hours before intake of study medication; any medication known to interact with either of the study medications (eg, lithium-containing products, diuretics, methotrexate, uricosurics, digoxin, pentoxifylline, ticlopidine, phenobarbital, phenytoin, carbamazepine, chloramphenicol, rifampicin, zidovudine); and any medication known to accelerate or decelerate gastric emptying.

Study Design

This was a randomized, double-blind, double-dummy, placebo-controlled, parallel-group trial. Patients were recruited at 7 clinics in Moscow, Russia, and 10 clinics in Kyiv and Luganslk, Ukraine. Patients were allocated by permuted block randomization (block size of 5) to receive a single dose of aspirin 500 or 1000 mg, acetaminophen 500 or 1000 mg, or placebo. Tablets of the 2 active drugs differed in shape and size; to preserve blinding, each patient received 2 glass bottles, one containing 2 tablets of aspirin 500 mg or matching placebo of identical color, size, and shape, and the other containing 2 tablets of acetaminophen 500 mg or matching placebo of identical color, size, and shape. The placebo group received 2 bottles containing two 500-mg tablets of aspirin placebo and two 500-mg tablets of acetaminophen placebo. Study medication consisted of the contents of both bottles (4 tablets), taken with 200 mL tap water. Medication was taken in the presence of the investigator or study nurse, who recorded the receipt of medication and compliance with the study protocol. No hot or cold drinks or meals were allowed during the 6-hour observation period. Water at room temperature was supplied to a limit of 1 L per patient but was not allowed within 10 minutes before measurement of body temperature.

Rescue medication of the investigator's choice was allowed at any time during the study, either at the patient's request or at the investigator's discretion. However, both patients and investigators were encouraged to wait until 4 hours after dosing of study medication. The specific rescue medication and its time of intake were recorded.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its amendments[10] and with the good clinical practice guidelines.[11] The study was approved by the State Pharmacological Committee of the Ukrainian Ministry of Health and the Ethics Committee in Kyiv, Ukraine, and the Ethics Committee of the Federal Board for Quality Control, Effectiveness, and Safety of Drugs, Moscow, Russia. All patients provided written informed consent before enrollment.

Study End Points

The primary efficacy variable was the AUC for the change in orally measured body temperature from baseline until 4 hours after dosing (in accordance with the approved dosing for both drugs [1–2 tablets q4–6h]). Secondary efficacy variables were the maximum temperature difference between baseline and the lowest measured body temperature, the time to the maximum temperature difference, the temperature difference between baseline and each measured time point after dosing, and the intensity of the URTI symptoms of headache, frontal and maxillary sinus sensitivity to percussion, sore throat, achiness, and feverish discomfort. Safety and tolerability were assessed based on the incidence and nature of reported adverse events.

Study Assessments

At screening, patients provided demographic data, a medical history, and details of their medication use during the prestudy period. Women of childbearing potential underwent pregnancy testing. Physical examination included sublingual measurement of body temperature using a certified Tempa-Dot (3M HealthCare, St. Paul, Minnesota) single-use clinical thermometer. Instructions in the use of the thermometer were translated into Russian, double-checked, and approved, and investigators attended a training session before the start of the study. Oral temperature was measured again at baseline (directly before intake of study medication) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, and 6 hours after treatment.

Headache, frontal and maxillary sinus sensitivity to percussion, sore throat, achiness, and feverish discomfort were rated by patients using an ordinal scale (from 0 = none to 10 = severe) at baseline and again at 2, 4, and 6 hours after treatment. Patients remained at the clinic for the entire 6-hour observation period. Adverse events were recorded throughout this period. After 6 hours, a physical examination was performed and patients were discharged.

Statistical Analysis

The study was conducted according to a 3-stage group sequential test plan with 2 interim analyses (O'Brien/Fleming type). Statistical testing and adaptive sample-size recalculation at each interim analysis were preplanned using the inverse normal methodology described by Lehmacher and Wassmer.[12] With regard to the primary efficacy variable, the following objectives were tested consecutively in an a priori fixed order: (1) the superiority of aspirin 1000 mg versus placebo; (2) the superiority of aspirin 500 mg versus placebo; (3) the noninferiority of aspirin 500 mg versus acetaminophen 500 mg; and (4) the noninferiority of aspirin 1000 mg versus acetaminophen 1000 mg. The noninferiority margin was defined as 15% of the treatment effect of acetaminophen 1000 mg (0.6165 C · h). The 2-sample t test (1-sided) was used for confirmatory testing in the interim analyses as well as in the final analysis. The overall type I error rate of $\alpha = 0.025$ was preserved by the statistical methods used. The results of all further analyses were interpreted in an exploratory fashion.

The primary analysis was based on the full analytic set, including all randomized patients who took study medication and provided any efficacy data (intent-to-treat [ITT] analysis). Patients with major protocol violations or incomplete documentation of the primary efficacy variable were excluded from the per-protocol (PP) analysis.

An independent data monitoring committee, working according to specific standard operating procedures, was responsible for the interim analyses and the decisions regarding sample-size adaptation and early discontinuation of the study. The sample size was estimated prospectively as follows: assuming equal AUCs for aspirin 500 mg and acetaminophen 500 mg, as well as for aspirin 1000 mg and acetaminophen 1000 mg, with a common SD of 3.5 C · h and a noninferiority margin of 1.5 C · h, a power of 80% would be achieved if the 3 stages of the group sequential test plan consisted of $n1 = n2 = n3 = 30$ patients per treatment group, resulting in 90 patients per treatment group and a total of 450 patients (overall type I error rate, 0.025, 1-sided t test).

RESULTS

Study Population

All 4 null hypotheses were rejected after the second interim analyses, and the independent data monitoring committee considered it unethical to continue to withhold active treatments from patients and recommended that the study be completed without enrollment of the originally proposed sample of 450 patients (90 in each treatment arm). Therefore, only 392 of 529 screened patients were randomized to the study groups. All took study medication and provided efficacy data. From this ITT data set, 6 patients were excluded for incomplete or inadequate documentation of the primary end point at 4 hours after dosing, creating a PP data set of 386 patients. In the ITT population, 78 patients each received aspirin 500 mg, aspirin 1000 mg, and placebo, and 79 patients each received acetaminophen 500 mg and acetaminophen 1000 mg.

Demographic and baseline characteristics were comparable between the 5 treatment groups (Table I): 51% of patients were male, and the mean age of patients was 37.4 years. The mean baseline oral temperature for the 5 treatment groups was 38.96°C (range, 38.86–39.02°C). The baseline intensity of the URTI symptoms was comparable between groups, although there were large differences in the intensity of specific symptoms. Ratings of headache, achiness, and feverish discomfort were high at baseline (6.46, 5.96, and 6.95, respectively), whereas the ratings of sore throat and frontal and maxillary sinus sensitivity to percussion were considerably lower (3.25 and 1.55, respectively).

Efficacy

Figure 1 shows the time course of orally measured body temperature, and Figure 2 shows the time course of the reduction in body temperature from baseline. Both doses of both active treatments were effective compared with placebo, and a distinct dose-response relationship was observed for both. In each case, the 1000-mg dose provided a significantly higher reduction in body temperature compared with the 500-mg dose ($P < 0.001$), with no statistically significant dif-

Table I. Demographic and baseline characteristics of the intent-to-treat population.

Characteristic	Aspirin 500 mg (n = 78)	Aspirin 1000 mg (n = 78)	Acetaminophen 500 mg (n = 79)	Acetaminophen 1000 mg (n = 79)	Placebo (n = 78)
Sex, no. (%)					
Male	36 (46.2)	47 (60.3)	36 (45.6)	41 (51.9)	41 (52.6)
Female	42 (53.8)	31 (39.7)	43 (54.4)	38 (48.1)	37 (47.4)
Age, mean (SD), y	36.7 (12.1)	36.8 (12.2)	37.8 (12.4)	37.0 (11.3)	38.7 (12.4)
Height, mean (SD), cm	172.7 (9.3)	174.8 (9.7)	173.3 (9.0)	172.9 (9.9)	173.7 (9.5)
Body weight, mean (SD), kg	72.9 (14.1)	76.5 (14.0)	74.3 (13.1)	73.7 (14.0)	74.0 (12.5)
Body mass index, mean (SD), kg/m^2	24.4 (3.9)	25.0 (4.3)	24.7 (4.0)	24.6 (3.9)	24.5 (3.3)
Race, no. (%)					
White	78 (100)	77 (98.7)	78 (98.7)	78 (98.7)	78 (100)
Other	–	1 (1.3)	1 (1.3)	1 (1.3)	–
Oral body temperature, mean (SD), °C	39.01 (0.31)	38.94 (0.26)	39.02 (0.34)	38.99 (0.31)	38.86 (0.31)
URTI symptoms, mean (SD) intensity*					
Headache	6.44 (2.10)	6.60 (2.05)	6.29 (2.48)	6.86 (2.06)	6.12 (2.12)
Frontal and maxillary sinus sensitivity to percussion	1.47 (1.93)	1.63 (2.23)	1.53 (1.88)	1.49 (1.83)	1.64 (2.09)
Sore throat	3.32 (2.62)	2.95 (2.72)	3.22 (2.73)	3.49 (2.51)	3.26 (2.57)
Achiness	6.12 (1.94)	6.21 (2.37)	5.70 (2.66)	6.19 (2.44)	5.62 (2.25)
Feverish discomfort	6.96 (1.43)	7.14 (1.74)	6.91 (1.71)	7.23 (1.48)	6.53 (1.54)

URTI = upper respiratory tract infection.
*Rated by patients on an ordinal scale from 0 = none to 10 = severe.

ferences in the AUC for change from baseline body temperature from 0 to 4 hours after dosing between aspirin 500 mg (AUC = 3.18; 95% CI, 2.78–3.57) and acetaminophen 500 mg (AUC = 3.13; 95% CI, 2.77–3.49), or between aspirin 1000 mg (AUC = 4.26; 95% CI, 3.84–4.68) and acetaminophen 1000 mg (AUC = 4.11; 95% CI, 3.73–4.49) (Figure 3). All active treatments were significantly better than placebo (AUC = 0.76; 95% CI, 0.38–1.13; $P < 0.001$). Aspirin 500 mg was noninferior to acetaminophen 500 mg ($P < 0.008$), and aspirin 1000 mg was noninferior to acetaminophen 1000 mg ($P < 0.004$). Temperature reduction started as early as 30 minutes after treatment with all active medications and persisted for a minimum of 6 hours, as all active treatments continued to be significantly different from placebo at 6 hours.

The mean maximum temperature difference between baseline and the lowest measured temperature after dosing was greatest for aspirin 1000 mg (1.67°C) and acetaminophen 1000 mg (1.71°C). These were significantly greater than the differences for the corresponding 500-mg doses, and all active treatments were significantly different from placebo (1.32°C, 1.25°C, and 0.63°C for aspirin 500 mg, acetaminophen 500 mg, and placebo, respectively; $P < 0.001$). The mean time to the maximum temperature difference was highest with acetaminophen 1000 mg (213 minutes), intermediate with aspirin 1000 mg (174 minutes) and placebo (170 minutes), and lowest with aspirin 500 mg (159 minutes) and acetaminophen 500 mg (154 minutes) (Table II).

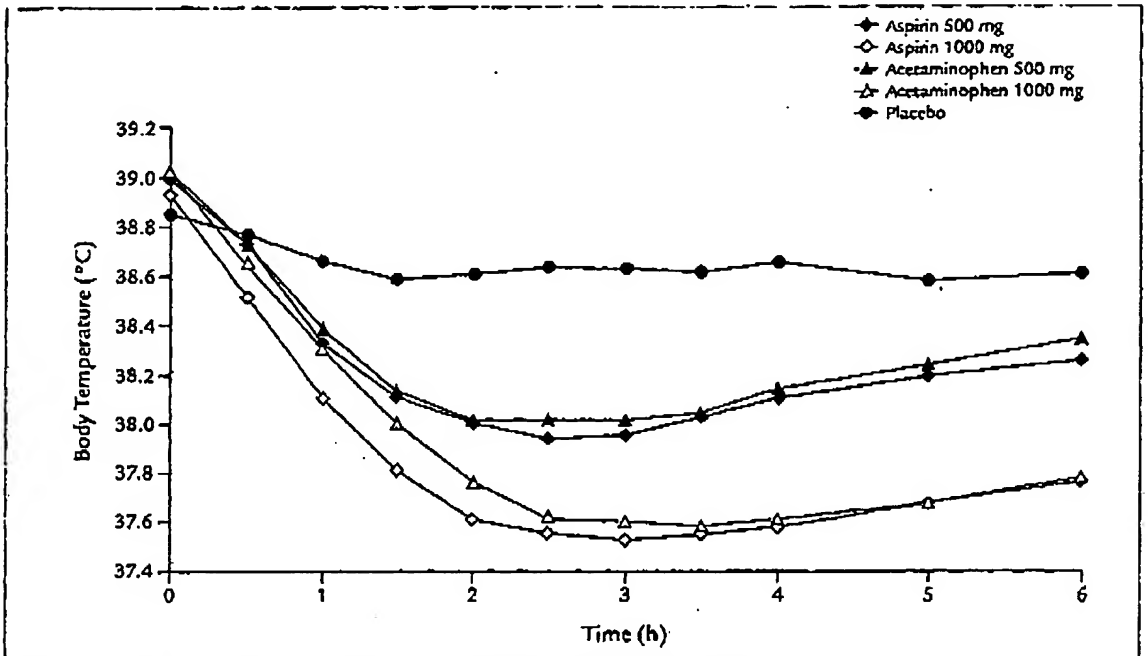

Figure 1. Time course of orally measured body temperature (mean values).

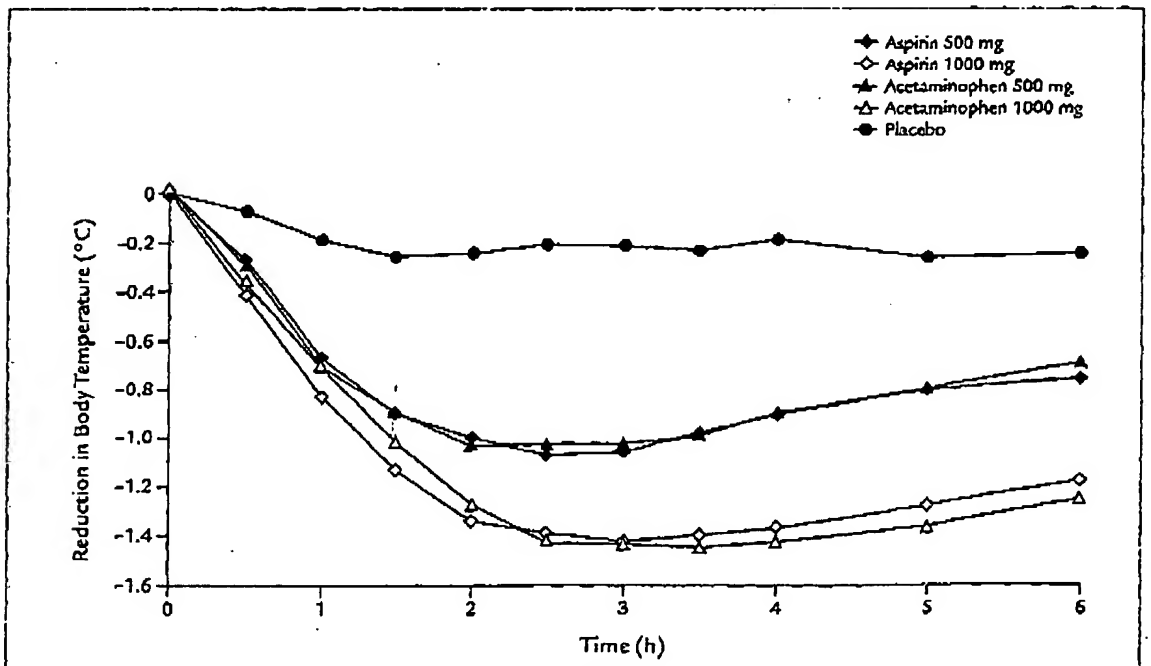

Figure 2. Time course of reduction in orally measured body temperature (mean values).

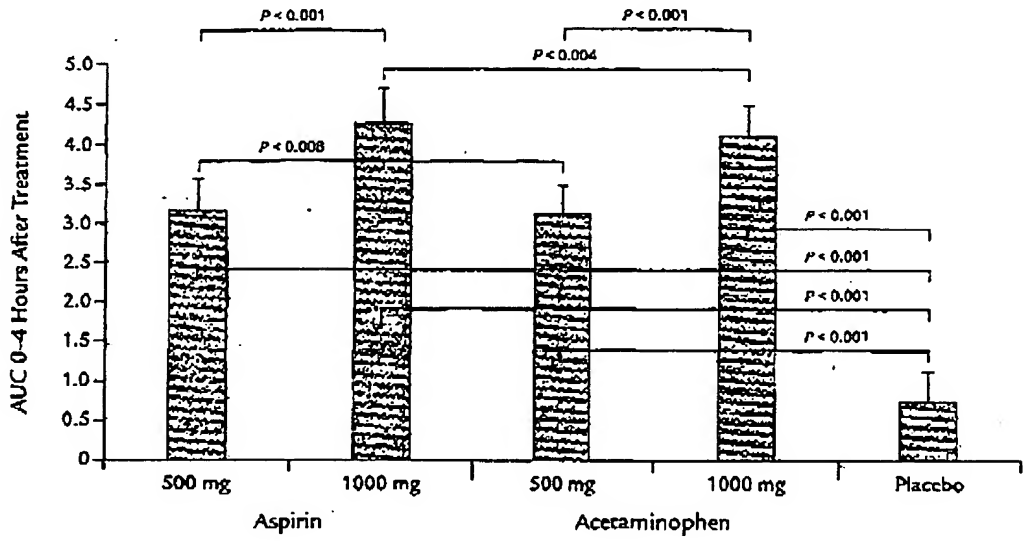

Figure 3. AUC for the change in orally measured body temperature from 0 to 4 hours after treatment (mean [95% CI]). *P* values are for noninferiority between the indicated treatment groups (1-sided *t* test).

Table III summarizes the mean intensity of URTI symptoms at baseline and at 2, 4, and 6 hours. Whereas the total mean intensities of headache, achiness, and feverish discomfort were meaningful (score >6 on the 11-point scale) at baseline (6.46, 5.96, and 6.95, respectively), the baseline total mean intensity of frontal and maxillary sinus sensitivity to percussion and sore throat was low (1.55 and 3.25, respectively). Headache intensity decreased significantly in all active-treatment groups at all time points ($P < 0.001$ vs placebo). Achiness was significantly reduced compared with placebo at all time points with aspirin 1000 mg and acetaminophen 1000 mg (all, $P < 0.001$) and at 2 and 4 hours after dosing with aspirin 500 mg and acetaminophen 500 mg (both, $P < 0.01$). Feverish discomfort was reduced at all time points with aspirin 1000 mg and acetaminophen 1000 mg (all, $P < 0.001$ vs placebo), at 2 and 4 hours after dosing with aspirin 500 mg and acetaminophen 500 mg ($P < 0.001$ vs placebo), and at 6 hours after dosing with these lower doses ($P < 0.015$ and $P < 0.017$, respectively). There were no significant decreases in frontal and maxillary sinus sensitivity to percussion or sore throat with either dose of active treatment at any time point.

Use of rescue medication varied between treatment groups. In the placebo group, 50.0% of patients took rescue medication. Patients in the aspirin and acetaminophen groups used significantly less rescue medication (24.4% aspirin 500 mg, 5.1% aspirin 1000 mg, 17.7% acetaminophen 500 mg, and 5.1% acetaminophen 1000 mg; all, $P < 0.001$ vs placebo).

Because the difference between the ITT and PP populations was only 6 patients, the PP analysis was performed for the primary efficacy end point only. As would be expected, the ITT results were confirmed by the results of the PP analysis.

Tolerability

All treatments were well tolerated. No serious or severe adverse events were reported. The proportion of patients reporting adverse events was lowest in the groups that received aspirin 500 mg (15.4%) and acetaminophen 500 mg (12.7%), intermediate in the placebo group (21.8%), and highest in the groups that received aspirin 1000 mg (30.8%) and acetaminophen 1000 mg (29.1%). The differences between the active treatments and placebo did not reach statistical significance. All adverse events were of mild or moderate intensity. The most frequently reported adverse event was

Table II. Mean (95% CI) maximum temperature differences from baseline and mean time to reach maximum temperature difference.

Treatment	Maximum Temperature Reduction, °C	Mean Time to Maximum Temperature Reduction, min
Aspirin		
500 mg	1.32 (1.21–1.44)*	159 (139–179)
1000 mg	1.67 (1.53–1.80)*†	174 (156–193)
Acetaminophen		
500 mg	1.25 (1.13–1.36)*	154 (137–171)
1000 mg	1.71 (1.60–1.82)*‡	213 (193–233)
Placebo	0.63 (0.50–0.76)	170 (146–194)

*$P < 0.001$ versus placebo, 1-sided t test.
†$P < 0.001$ versus aspirin 500 mg, 1-sided t test.
‡$P < 0.001$ versus acetaminophen 500 mg, 1-sided t test.

increased sweating (7.7% aspirin 500 mg, 19.2% aspirin 1000 mg, 6.3% acetaminophen 500 mg, 13.9% acetaminophen 1000 mg, 1.3% placebo). Gastrointestinal adverse events were also common (3.8%, 12.8%, 5.1%, 8.9%, and 3.8%, respectively). Adverse events that were judged by the investigator to have a possible relationship to study medication affected the following proportions of patients in the respective treatment groups: 10.3%, 29.5%, 11.4%, 25.3%, and 5.1%. The differences in the incidence of treatment-related adverse events were significant between acetaminophen 500 and 1000 mg compared with placebo (both, $P < 0.001$) (Table IV).

DISCUSSION

This study investigated the antipyretic effect of 2 OTC analgesics, aspirin and acetaminophen, each at single doses of 500 and 1000 mg, in adult patients with fever (oral temperature ≥38.5°C) and other symptoms of URTI. Reduction in fever and relief of other URTI symptoms were measured over a period of 6 hours, in accordance with the recommended use of these drugs. All 4 active treatments were significantly more effective in reducing fever compared with placebo ($P < 0.001$). The antipyretic effect started as early as 30 minutes after dosing and lasted for at least 6 hours. At equal doses, no statistically significant differences were observed between aspirin and acetaminophen; however, the higher dose of each agent was significantly more effective than the lower dose with respect to the mean reduction in temperature and duration of effect (both, $P < 0.001$). Based on the results of this study, aspirin and acetaminophen can be considered comparable with respect to reduction of fever in patients with URTI.

The results of this study are consistent in part with those of a single-dose study by Gehanno et al,[13] in which diclofenac and acetaminophen were compared in adult patients with acute febrile sore throat and an oral body temperature ≥38°C, and with those of a study by Grebe et al,[14] in which diclofenac and ibuprofen were compared in adults with influenzalike symptoms and an oral body temperature of ≥38.1°C. As in the present study, maximum reductions in oral body temperature were achieved between 2.5 and 3 hours after dosing. In this study, the time to the maximum temperature difference from baseline was longer with acetaminophen 1000 mg (213 minutes) compared with the other study treatments. Mean maximum temperature reductions were considerably higher in the present study than in Gehanno et al, who reported decreases of −0.65°C for acetaminophen 1000 mg and −0.7°C for diclofenac 25 and 12.5 mg, and in Grebe et al, who reported reductions of 0.85°C for diclofenac 25 mg and 0.76°C for ibuprofen 400 mg. The reductions in the present study were 1.32°C and 1.25°C for aspirin 500 mg and acetaminophen 500 mg, respectively, and 1.67°C and 1.71°C for aspirin 1000 mg and acetaminophen 1000 mg, respectively.

The comparability of aspirin 500 mg with acetaminophen 500 mg and aspirin 1000 mg with acetaminophen 1000 mg was supported by the results of the analyses of other URTI symptoms. Significant improvements were seen in headache, achiness, and feverish discomfort with all active treatments at most time points ($P < 0.001$), whereas frontal and maxillary sinus sensitivity to percussion and sore throat showed no statistically significant or clinically relevant improvement. However, the intensity of the latter symptoms was low at baseline, whereas the intensity of the symptoms that showed measurable improvement were higher at baseline. Grebe et al[14] also reported that such influenzalike symptoms as headache, feverishness, and muscle/joint aches and pains were relieved by treatment with diclofenac and ibuprofen.

The lack of effect of aspirin and acetaminophen on frontal and maxillary sinus sensitivity to percussion and

Table III. Intensity of symptoms of upper respiratory tract infection, rated by patients on a scale from 0 = none to 10 = severe. Values are mean (SD).

	Aspirin		Acetaminophen		
Symptom/Time Point	500 mg	1000 mg	500 mg	1000 mg	Placebo
Headache					
0 Hours	6.44 (2.10)	6.60 (2.05)	6.29 (2.48)	6.86 (2.06)	6.12 (2.12)
2 Hours	4.36 (1.94)*	4.00 (1.85)*	4.28 (1.93)*	4.29 (1.99)*	5.72 (1.93)
4 Hours	4.03 (1.99)*	3.58 (2.01)*	4.33 (2.14)*	3.62 (1.94)*	5.76 (2.14)
6 Hours	4.41 (2.18)*	3.76 (2.26)*	4.63 (2.19)*	3.95 (2.20)*	5.78 (2.06)
Frontal and maxillary sinus sensitivity to percussion					
0 Hours	1.47 (1.93)	1.63 (2.23)	1.53 (1.88)	1.49 (1.83)	1.64 (2.09)
2 Hours	1.13 (1.46)	1.14 (1.91)	1.15 (1.54)	1.11 (1.50)	1.58 (2.00)
4 Hours	1.04 (1.51)†	1.08 (1.85)	1.19 (1.63)	0.96 (1.30)‡	1.68 (2.13)
6 Hours	1.17 (1.56)	1.13 (1.96)	1.28 (1.67)	1.09 (1.52)	1.65 (2.08)
Sore throat					
0 Hours	3.32 (2.62)	2.95 (2.72)	3.22 (2.73)	3.49 (2.51)	3.26 (2.57)
2 Hours	2.78 (2.25)	2.24 (2.35)†	2.77 (2.41)	2.95 (2.31)	3.08 (2.36)
4 Hours	2.64 (2.19)	2.19 (2.27)†	2.61 (2.29)	2.70 (2.19)	2.95 (2.37)
6 Hours	2.68 (2.21)	2.21 (2.28)†	2.80 (2.41)	2.68 (2.17)	3.01 (2.33)
Achiness					
0 Hours	6.12 (1.94)	6.21 (2.37)	5.70 (2.66)	6.19 (2.44)	5.62 (2.25)
2 Hours	4.60 (1.85)‡	3.65 (2.11)*	4.41 (2.08)‡	4.30 (2.08)*	5.36 (2.06)
4 Hours	4.31 (1.97)‡	3.19 (2.25)*	4.25 (2.25)‡	3.46 (2.14)*	5.33 (2.21)
6 Hours	4.77 (2.04)	3.36 (2.47)*	4.67 (2.35)	3.54 (2.43)*	5.26 (2.20)
Feverish discomfort					
0 Hours	6.96 (1.43)	7.14 (1.74)	6.91 (1.71)	7.23 (1.48)	6.53 (1.54)
2 Hours	5.00 (1.77)*	4.12 (2.23)*	4.92 (1.77)*	4.54 (1.70)*	6.21 (1.75)
4 Hours	4.75 (1.90)*	3.49 (2.36)*	4.96 (1.84)*	3.48 (2.11)*	6.08 (2.01)
6 Hours	5.29 (2.04)†	3.71 (2.56)*	5.35 (1.84)†	3.80 (2.48)*	6.00 (1.93)

*$P < 0.001$ versus placebo, 1-sided t test.
†$P < 0.025$ versus placebo, 1-sided t test.
‡$P < 0.01$ versus placebo, 1-sided t test.

Table IV. Incidence (%) of reported adverse events (AEs).

Treatment	Overall AEs	Increased Sweating	Gastrointestinal AEs	Drug-Related AEs
Aspirin				
500 mg	15.4	7.7	3.8	10.3
1000 mg	30.8	19.2	12.8	29.5*
Acetaminophen				
500 mg	12.7	6.3	5.1	11.4
1000 mg	29.1	13.9	8.9	25.3*
Placebo	21.8	1.3	3.8	5.1

*$P < 0.001$ versus placebo.

sore throat is not unexpected. Acute URTI is not a single disease entity but a syndrome composed of multiple symptoms that vary in severity and incidence according to the infectious agent and the patient.[15] For example, Eccles et al[15] reported a significant reduction in headache and muscle aches (both, $P < 0.01$) and a nonsignificant reduction in sinus pain; unlike the present study, however, there was a nonsignificant reduction in feverish discomfort, possibly explained by its low incidence in that study. On the other hand, the incidence of sore throat was low in the present study and its reduction nonsignificant, whereas in Eccles et al, sore throat was an inclusion criterion and was significantly reduced with aspirin compared with placebo ($P < 0.001$).

The incidence of adverse events in this study was comparable between active treatments. Both active treatments showed dose dependency. Whereas the proportion of placebo recipients reporting adverse events fell between the proportions in the groups receiving the 500- and 1000-mg doses of each active treatment, the percentage of placebo recipients with drug-related adverse events was lower compared with those in all active-treatment groups. The most common adverse event was increased sweating, which was more frequent at the higher dose of each active treatment and infrequent in the placebo group. This is not surprising, as sweating is associated with the antipyretic effects of aspirin and acetaminophen. The frequency of gastrointestinal adverse events was identical with aspirin 500 mg and placebo, higher with acetaminophen 500 mg, pronounced with acetaminophen 1000 mg, and highest with aspirin 1000 mg. No serious or severe adverse events were reported, supporting the good risk-benefit ratio of these antipyretic and analgesic drugs in patients with fever and the URTI symptoms of headache, achiness, and feverish discomfort.

CONCLUSIONS

In this single-dose study, aspirin 500 mg and 1000 mg were significantly more effective than placebo in reducing fever and other symptoms of URTI in adult patients. There were no significant differences in the antipyretic and symptom-relieving efficacy of equal doses of aspirin and acetaminophen over the 6-hour observation period. The safety profile and tolerability of aspirin and acetaminophen were also comparable.

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